(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 260 979 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **15.05.91** (51) Int. Cl.5: **C07H 13/04**, C07H 13/08

(21) Application number: **87308260.6**

(22) Date of filing: **17.09.87**

(54) Sucrose derivatives.

(30) Priority: **17.09.86 GB 8622345**

(43) Date of publication of application:
23.03.88 Bulletin 88/12

(45) Publication of the grant of the patent:
15.05.91 Bulletin 91/20

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 031 651
EP-A- 0 043 649

R.J. FERRIER et al.: "Monosaccharide Chemistry", pages 196-197, 1972, Penquin Books, Harmondsworth, GB;

CHEMISCHE BERICHTE, vol. 100, 1967, pages 2822-2836, Verlag Chemie Gmbh, Weinheim, DE; H. PAULSEN et al.: "Einfache Synthese von D-Idose aus D-Glucose durch mehrfache Acetoxonium-Ion-Umlagerungen. Darstellung eines stabilen Acetoxonium-Salzes der Tetraacetyl-Idose"

(73) Proprietor: **TATE & LYLE PUBLIC LIMITED COMPANY**
Sugar Quay Lower Thames Street
London, EC3R 6DQ(GB)

(72) Inventor: **Simpson, Philip John**
65 Rowan Road
Tadley Hampshire RG26 6RQ(GB)

(74) Representative: **Ablewhite, Alan James et al**
MARKS & CLERK 57/60 Lincoln's Inn Fields
London WC2A 3LS(GB)

EP 0 260 979 B1

Description

This invention relates to novel sucrose derivatives, the cyclic 4,6-orthoesters of sucrose, and in particular to a process for the preparation of sucrose 6-esters using the 4,6-orthoesters as starting materials. Sucrose 6-esters are key intermediates in one process for the preparation of sucralose, a high intensity sweetener having a sweetness several hundred times that of sucrose (British Patent specification No.1543167).

The preparation of sucralose involves the introduction of chlorine atoms into the 1'- and 6'-positions (i.e. the displacement of two of the three primary hydroxy groups) and at the 4- position (i.e. the displacement of a secondary hydroxy group). The third primary hydroxy group, at the 6- position, must remain unaffected.

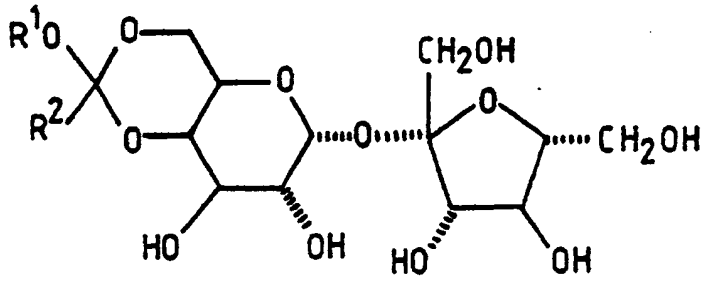
One important route to sucralose involves the preparation of 2,3,6,3',4'-penta-O-acetyl sucrose, in which the three hydroxy groups to be reacted are unprotected, while all the remaining hydroxy groups are protected. (See, for example. U.S. 4362869 or EP 31651B).

Selectively protecting the five positions not to be chlorinated, while exposing the three positions to be chlorinated, provides a number of technical difficulties. An alternative approach is to prepare a sucrose 6-ester which can, under appropriate conditions, be selectively chlorinated in the 4, 1' and 6' positions. A method of preparing sucrose 6 esters, and their conversion into sucralose is disclosed in GB-B-2079749. However, this process produces a mixture of acylated sucrose derivatives with substituents at one or more of the primary positions, but with the major proportion of 6-monoacylated sucrose. This is an attractive route to sucralose, but there is a need for a more selective method of producing sucrose 6-esters.

The present invention is based on the discovery that a novel range of sucrose derivatives can be readily obtained and that these derivatives, the 4,6-orthoesters, can be hydrolysed to give a mixture of sucrose 4- and 6-esters which can be simply isomerized to provide a high yield of 6-ester and the virtual absence of 4- ester.

Cyclic orthoesters of carbohydrates have been reported. The best known of these are bicyclic 1,2-glycopyranosyl derivatives which may be prepared from glycosyl halides and have been used as intermediates in the synthesis of disaccharides (Kochetkov & Bochkov in Methods in Carbohydrate Chemistry, VI, Academic Press New York and London 1972 p 480). Orthoesters at other positions are less well known, but Ferrier and Collins (in Monosaccharide Chemistry, Penguin Books, Harmondsworth, Middlesex 1972 p 196) mentioned that they may be prepared by the acid catalysed reactions of suitable carbohydrate diols and trialkyl orthoesters. It has now been found that the reaction of trialkyl orthoesters under acid catalysis with sucrose itself, surprisingly gives a 4,6-orthoester in the absence of other isomers and in good yield. These 4,6-orthoesters of sucrose are novel compounds.

The novel sucrose derivatives of use in the present invention are sucrose alkyl 4,6-orthoacylates, namely compounds of the general formula



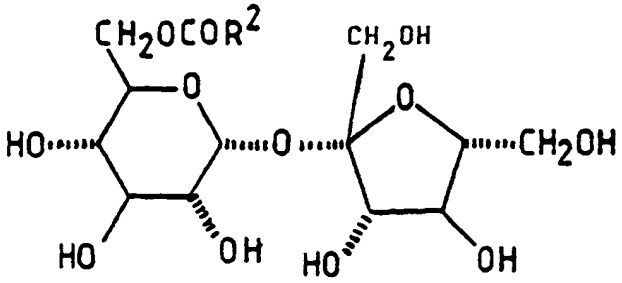
(I)

where R^1 represents an alkyl group, especially an alkyl group with 1-3 carbon atoms e.g. a methyl, ethyl or propyl group; and R^2 represents an alkyl or aryl group, preferably an alkyl group with 1-4 carbon atoms, e.g. a methyl, ethyl, propyl or butyl group, or a phenyl group. Particularly useful compound of the general formula I include sucrose methyl 4,6-orthoacetate, sucrose ethyl 4,6-orthoacetate, sucrose methyl 4,6-orthobutyrate and sucrose methyl 4,6-orthobenzoate. These novel compounds represent one feature of the present invention.

According to the present invention there is provided a process for the preparation of a sucrose 6-acylate comprising subjecting a sucrose alkyl 4,6-orthoacylate to mild aqueous acidic hydrolysis to provide a mixture of 4- and 6- monoesters of sucrose and then treating the ester mixture with a base to convert the

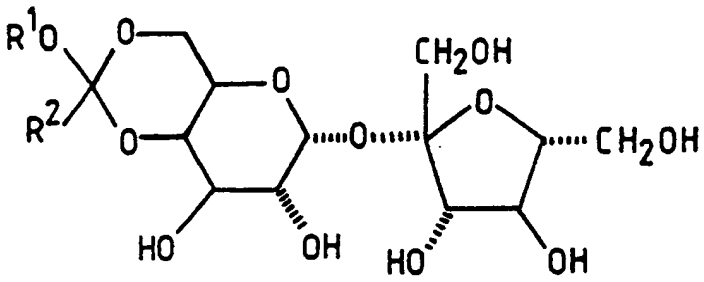
sucrose 4-ester into sucrose 6- ester.

In particular, there is provided a process for the preparation of a sucrose ester of the general formula II



(II)

in which R^2 represents an alkyl or aryl group, by treatment of an orthoester of the general formula I



(I)

in which R^1 represents an alkyl group and R^2 is as defined for formula II, under mild aqueous acidic conditions followed by treatment with a base.

The initial mildly acidic treatment can be effected in aqueous solution in the presence of a catalytic amount of an acid such as toluene p-sulphonic acid or hydrochloric acid. However, for preference, the reaction is carried out in solution in an inert polar organic solvent such as DMF or pyridine containing some water and an acid such as those mentioned above, or pyridine hydrochloride. The amount of water added should be an excess over that required theoretically, typically 3 to 10 molar equivalents based on the sucrose ester, e.g. 4 to 8 ME. The acid should be sufficient to give a pH of about 5 to 6. The reaction proceeds effectively at ambient temperature.

The reaction with a base, to isomerise the 4-ester to the 6-ester, can conveniently be effected in the same solution, simply by adding sufficient base to neutralise the acid and to provide a small excess. Typical bases of use include tertiary amines such as pyridine and its analogues and tertiary alkylamines such as t-butylamines. Again, the reaction proceeds at ambient temperature.

An exception to the above is the case of the orthobenzoate, where cleavage requires more forcing conditions (i.e. a lower pH and a temperature above ambient).

The method of the present invention provides an easy and selective route to sucrose 6- esters and, since these can be easily chlorinated, it also provides a simple direct route to sucralose itself. Thus, according to a further feature of the present invention there is provided a process for the preparation of sucralose comprising reacting sucrose to prepare a sucrose 6-ester, reacting the sucrose 6-ester with a chlorinating agent capable of effecting selective chlorination at the 4-,1' and 6'- positions, optionally peresterifying the sucralose 6-ester so formed and deesterifying the sucralose ester before or after the separation from the reaction mixture, and recovering sucralose,
characterised in that the formation of the sucrose 6-ester is effected by cleaving a sucrose alkyl 4,6-orthoacylate under mildly acidic aqueous conditions followed by treatment with a base.

The chlorination step can be effected using any of the suitable chlorinating systems, for example those disclosed in GB 2 079 749B, for example a reagent of the Vilsmeier type, i.e. an N,N-dialkyl-(chloromethaniminium) chloride; a triarylphosphine or triarylphosphite; or sulphuryl chloride. Another useful

chlorinating system is thionyl chloride in the presence of triphenyl phosphine oxide (see GB 2 182 039A)..

The sucrose 4,6-orthoesters used as starting materials can be prepared selectively by the direct reaction of sucrose with a trialkyl orthoester in a suitable inert organic solvent such as dimethyl formamide or pyridine, in the presence of an acid catalyst. The reaction is virtually complete within one hour at ambient temperature with only traces of sucrose and an intermediate component present. After neutralising (e.g. with a suitable ion exchange resin) and filtering, the product can be recovered as a clear colourless syrup by evaporation of the filtrate under vacuum. The relatively mild reaction conditions are not conducive to the formation of unwanted by-products.

According to the present invention there is further provided a method for the preparation of sucrose 4,6-orthoesters by the reaction of sucrose with a trialkyl orthoester in the presence or an acid catalyst in an inert organic solvent or suspending agent.

The catalyst can be any strong acid and we have found it convenient to use p-toluene sulphonic acid, pyridinium chloride or tosylate or toluene sulphonic acid.

The following Examples illustrate the invention.

Example 1

Preparation of sucrose methyl 4,6-orthoacetate

To a solution of sucrose (3.42 g) in dimethylformamide (27.5 ml) was added trimethyl orthoacetate (1.91 ml; 1.5 ME) and a catalytic amount of p-toluene sulphonic acid (25 mg). After one hour at ambient temperature, tlc (n-BuOH/EtOH/$H_2$0, 5:3:2) showed virtually complete reaction to a new compound (Rf 0.62) with only traces of sucrose (Rf 0.40) and an intermediate component (Rf 0.54) present. The solution was then neutralised using Amberlite IRA93(OH^-) ion exchange resin, filtered and the filtrate evaporated in vacuo to a clear colourless syrup (4.0 g). A sample of this material was acetylated by the conventional method using acetic anhydride in pyridine. The ^{1}H NMR spectrum of the acetate was consistent with the structure. The mass spectrum of the hexaacetate was also consistent with the structure, giving M^+ -OCH_3 = 619.

Example 2

Preparation of sucrose 6-acetate

Sucrose methyl 4,6-orthoacetate (1 g) was dissolved in water (10 ml), solution pH 5. After one hour at ambient temperature tlc (n-BuOH/EtOH/$H_2$0, 5:3:2) showed a major component at Rf 0.54 with only a trace of the orthoacetate (Rf 0.62) and a little sucrose (Rf 0.40) remaining. HPLC analysis of the solution after two hours showed, inter alia, major components with retention times of 3.46 (sucrose), 4.66 (sucrose 4-acetate) and 8.63 (sucrose 6-acetate) in the approximate ratios 7:49:43. Pyridine (1 ml) was then added to the aqueous solution. Periodical HPLC analysis showed an increase in sucrose 6-acetate concentration with time and a decrease in sucrose 4-acetate. After 4 hours the ratios of sucrose: sucrose 4-acetate: sucrose 6-acetate were 11:3:85. The solution was then concentrated to dryness and the residue was dissolved in pyridine and evaporated in vacuo to a syrup to remove residual water. A solution of the syrup in pyridine (10 ml) was stored overnight over molecular sieve (4 A) in preparation for chlorination as described in Example 3.

Example 3

Preparation of sucralose

Thionyl chloride (1.52 ml, 8 ME) was added to a solution of triphenylphosphine oxide (2.17 g, 3 ME) in pyridine (8 ml). The solution was heated to 50° before adding the solution of sucrose 6-acetate in pyridine (about 1 g in 10 ml) from Example 2. The mixture was heated to 95° and held at this temperature for one

hour. The mixture was then acetylated in the conventional manner, using acetic anhydride in pyridine. Tlc (diethyl ether/petrol 4:1) of the acetylated reaction mixture showed a major component corresponding to sucralose pentaacetate, a trace of tetrachloro galactosucrose tetraacetate and base line material. The sucralose pentaacetate was separated by crystallisation, taken up in methanol and deacetylated by treatment with sodium methoxide in the conventional manner to yield sucralose (about 0.5 g).

Example 4

Preparation of sucrose methyl 4,6-orthobutyrate (characterised as the hexaacetate)

A suspension of sucrose (10g) in pyridine (50 ml) was treated with trimethyl orthobutyrate (5.2 ml: 1.1 ME) and pyridinium tosylate (500 mg) at 75° for 2.5 hours. The resulting solution was cooled to 30° and acetic anhydride (35 ml) was added, allowing the temperature to rise to 60°. After 1 hour at 60°, the solution was cooled to room temperature and methanol (20 ml) was added. The solution was then concentrated to dryness, dissolved in ethyl acetate (50 ml), and evaporated onto silica gel (Merck 7734).

Column chromatography, eluting with diethyl ether-petroleum ether 40-60° (2:1) gave the pure sucrose methyl 4,6,orthobutyrate hexaacetate (16.2 g, 82%) which was recrystallised from diethyl ether-petroleum ether (40-60°) mp 84-85°; $[\alpha]_D$ + 55.2° (c 2.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$).

δ ppm				Hz
5.66	d	1H	H-1	$J_{1,2}$ 3.9
5.44	d	1H	H-3'	$J_{3',4'}$ 5.7
5.38	dd	1H	H-4'	$J_{3',4'}$ 5.7 / $J_{4',5'}$ 5.7
5.37	dd	1H	H-3	$J_{2,3}$ 10.0/$J_{3,4}$ 9.9
4.82	dd	1H	H-2	$J_{1,2}$ 3.9/$J_{2,3}$ 10.0
3.89	dd	1H	H-4	$J_{3,4}$ 9.9/$J_{4,5}$ 9.7
3.83-4.33	multiplets	8H	H-5, H-6(X2), H-1'(x2), H-5', H-6'(X2)	
3.26	s	3H	$-OCH_3$	
2.19	s	3H	-OAc	
2.12	s	3H	-OAc	
2.11	s	3H	-OAc	
2.10	s	3H	-OAc	
2.08	s	3H	-OAc	
2.06	s	3H	-OAc	
1.70	m	2H	$-\underline{CH_2}CH_2CH_3$	
1.40	m	2H	$-CH_2\underline{CH_2}CH_3$	
0.89	t	3H	$-CH_2CH_2\underline{CH_3}$	

EI mass spectrum MW 678

m/e	
	679 MH^+
	647 MH^+ - MeOH
	331 F^+OAc_4 & $OBuG^+OAc_2$

By an analogous method. using the corresponding trialkyl ortnoesters, the following compounds were prepared:

Sucrose methyl 4,6-orthoacetate hexaacetate [4,6-O-(1-methoxyethylidene)-sucrose hexaacetate]

cryst.diethyl ether/petroleum ether 40-60°

mp 79-81° $[\alpha]_D$ + 61.0° (c 2.0, $CHCl_3$)

δ ppm					Hz
5.66	d	1H	H-1	$J_{1,2}$	3.9
5.44	d	1H	H-3'	$J_{3',4'}$	5.5
5.39	dd	1H	H-3	$J_{2,3}$	9.8 / $J_{3,4}$ 9.8
5.37	dd	1H	H-4'	$J_{3',4'}$	5.5 / $J_{4',5'}$ 5.5
4.81	dd	1H	H-2	$J_{2,3}$	9.8 / $J_{1,2}$ 3.9
4.30-3.84	m	9H	H-4, H-5, H-6(X2), H-1'(X2), H-5', H-6(X2)		
3.29	s	3H	-OMe		
2.20	s	3H	-OAc		
2.12	s	3H	-OAc		
2.11	s	3H	-OAc		
2.10	s	3H	-OAc		
2.08	s	3H	-OAc		
2.07	s	3H	-OAc		
1.45	s	3H	-Me		

EI mass spectrum MW 650

m/e	651	MH^+
	619	MH^+-MeOH
	331	F^+OAc_4
	303	$OAcG^+OAc_2$

Sucrose ethyl 4,6-orthoacetate hexaacetate [4,6-O-(1-ethoxyethylidene)-sucrose hexaacetate]

cryst.diethyl ether - petroleum ether 40-60°

mp 93-95° $[\alpha]_D$ + 59.2° (c 2.0, $CHCl_3$)

^1H NMR ($CDCl_3$)

δ ppm					Hz
5.64	d	1H	H-1	$J_{1,2}$	3.8
5.43	d	1H	H-3'	$J_{3',4'}$	5.6
5.38	dd	1H	H-3	$J_{2,3}$	9.9 / $J_{3,4}$ 10.2
5.36	dd	1H	H-4'	$J_{3',4'}$	5.6/$J_{4',5'}$ 5.6
4.82	dd	1H	H-2	$J_{2,3}$	9.9/$J_{1,2}$ 3.8
4.33-3.85	m	9H	H-4, H-5, H-6(X2), H-1'(X2), H-5', H-6'(X2)		
3.51	s	2H	$-O\underline{CH_2}CH_3$		
2.20	s	3H	-OAc		
2.12	s	3H	-OAc		
2.11	s	3H	-OAc		
2.10	s	3H	-OAc		
2.08	s	3H	-OAc		
2.07	s	3H	-OAc		
1.46	s	3H	$-CH_3$		
1.26	t	3H	$-OCH_2\underline{CH_3}$	$J_{7,}$	

EI mass spectrum MW 664

m/e 665	MH^+
619	MH^+-EtOH
331	F^+OAc_4
317	$OAcG^+OAc_2$

Sucrose methyl 4,6-orthobenzoate hexaacetate

Syrup $[\alpha]_D$ + 40.8° (c 2.0, $CHCl_3$)

^1H NMR ($CDCl_3$)

δ ppm				Hz
7.52-7.28	m	5H	Ph	
5.71	d	1H	H-1	$J_{1,2}$ 3.9
5.51	dd	1H	H-3	$J_{2,3}$ 10.0 / $J_{3,4}$ 9.8
5.44	d	1H	H-3'	$J_{3',4'}$ 5.6
5.37	dd	1H	H-4'	$J_{3',4'}$ 5.6/$J_{4'5'}$ 5.7
4.91	dd	1H	H-2	$J_{1,2}$ 3.9/$J_{2,3}$ 10.0
4.08	dd	1H	H-4	$J_{3,4}$ 9.8/$J_{4,5}$ 9.4
4.04-4.30	m	8H	H-5, H-6(X2), H-1'(X2), H-5', H-6'(X2)	
3.06	s	3H	$-OCH_3$	
2.17	s	3H	-OAc	

2.12	s	3H	-OAc
2.11	s	3H	-OAc
2.10	s	3H	-OAc
2.09	s	3H	-OAc
2.02	s	3H	-OAc

EI mass spectrum MW 712

m/e	681	MH^+-MeOH
	365	$oBzG^+OAc_2$
	331	F^+OAc_4

Example 5

Cleavage of orthoesters

The procedure of Example 1 was carried out. Then, instead of the procedure of Example 2, the following method was used for the cleavage step:-

Once orthoester formation was complete, addition of 10% by volume of water (8ME based on sucrose) to the DMF solution, without neutralisation of the p-toluene sulphonic acid, gave a pH of 5.5. Cleavage of the orthoester occurred cleanly under these conditions but required at least 1 hour, allowing a noticeable amount of sucrose to be regenerated. By increasing the concentration of acid from the original 4 up to 6mg/g sucrose, the cleavage time was reduced to approximately 20 minutes and considerably less sucrose was regenerated (see Table 1). When the added water was halved to 5% (4ME), cleavage was almost as rapid but acetate migration was slower.

TABLE 1

Effect of acid and water concentration on the rate of orthoester cleavage in DMF solution

TsOH used (mg/g sucrose)	water added (ME)	time within which cleavage was completed (min)
4	8	70
6	8	20
6	4	25

Example 6

Acetate migration in DMF

In a modification of the method of Example 2, t-butylamine was used instead of pyridine to effect the acetate migration. Addition of 2.5% by volume to the wet DMF solution raised the pH to approximately 9. Under these conditions, acetate migration was complete within 1 hour, when HPLC indicated 87% sucrose 6-acetate, 3% sucrose 4-acetate and 10% sucrose to be present. (See Table 2). Reduction of the t-butylamine to 1.25%, or of the water to 5%, slowed the migration considerably, allowing a build up in the sucrose concentration. When migration was complete, the solution was concentrated under vacuum to a viscous syrup from which most of the DMF was removed by co-evaporation with toluene.

TABLE 2

Effect of t-butylamine and water concentration on the rate of acetate migration

$t\text{-BuNH}_2$ % by vol	H_2O % by vol	Time after addition of $t\text{-BuNH}_2$ (min)	Carbohydrate Composition % by HPLC S4A	S6A	S
		0	31.6	56.4	12.0
		30	25.0	62.8	12.2
1.25	5	120	10.1	76.8	13.0
		180	6.4	80.2	13.3
			31.3	56.9	11.8
		30	18.5	67.5	14.0
2.5	5	60	9.2	75.3	15.5
		135	3.2	80.6	16.1
		0	37.5	52.5	9.9
2.5	10	30	13.4	76.2	10.4
		60	2.1	86.9	11.0

S = sucrose, S4A = sucrose 4-acetate, S6A = sucrose 6-acetate

Example 7

Preparation of Sucrose 6-acetate

The procedures of Examples 5 and 6 were combined as follows:

A stirred suspension of sucrose (50g) in DMF (200ml) was treated with trimethyl orthoacetate (21ml: 1.1ME) and p-toluene sulphonic acid (300mg) at 20°C. After 2.5 hours, water (20ml: 8ME) was added to the clear solution. After a further 20 min., t-butylamine (5ml) was added. Stirring was continued for a further 1 hour before the mixture was concentrated under vacuum. DMF was removed by repeated co-evaporation with toluene (2x200ml, approximately) to leave crude sucrose 6-acetate as a thick colourless syrup.

Yield approximately 83g (still containing 25% DMF).

Approximate carbohydrate composition: sucrose 6-acetate; 87%, sucrose 4-acetate; 3%, sucrose; 10%.

The whole sequence was monitored by HPLC using a Zorbax NH_2 column, eluting with aqueous acetonitrile (85% v/v) at 1.5ml/min and using 2 µl injections of neat reaction mixture.

Example 8

Preparation of 100 g batches of sucrose 6-acetate in DMF

Five (100g) batches of sucrose 6-acetate were produced using the following method of preparation.

Sucrose (100g; icing sugar dried in vacuum oven for 24 hours at 60°C), trimethyl orthoacetate (48ml, 1.25 ME) and p-toluene sulphonic acid (600mg) were suspended in DMF (400ml) and the mixture was

stirred at room temperature (20-22° C) for 3 hours. The progress of the reaction was monitored by HPLC. The reaction mixture became clear after 1.25 hours. At that point the first sample for HPLC was taken out. The first stage of the reaction was considered complete when consecutive traces were found to be indistinguishable.

At this stage water (40ml, 8ME) was added to the reaction mixture at room temperature to cleave the 4,6-orthoacetate ring. According to HPLC the cleavage of orthoacetate ring to a mixture of sucrose 4- and 6-acetates was complete in approximately 1 hour.

In order to migrate the 4-acetate to the 6-position, tert-butylamine (10 ml) was added and the reaction mixture stirred at ambient temperature for 1.25 hours.

when HPLC indicated that no further migration was taking place the reaction mixture was concentrated to a syrup under reduced pressure at 800° - 85° C.

Average analysis of product:

weight	154g;

carbohydrate composition by HPLC

sucrose 6-acetate	84%
sucrose 4-acetate	4%
sucrose	12%

residual solvents:

DMF	24%
methanol	0.1%
toluene	1.0%
water	1.5%

The product could be used for chlorination to produce sucralose as in Example 3 above.

A sample of sucrose 6-acetate was purified by crystallisation from methanol to give mp 94-96°;
$[\alpha]_n$ + 60.3° (c 2.0, H_2O)
^{13}C NMR (DMSO-d_6) ppm

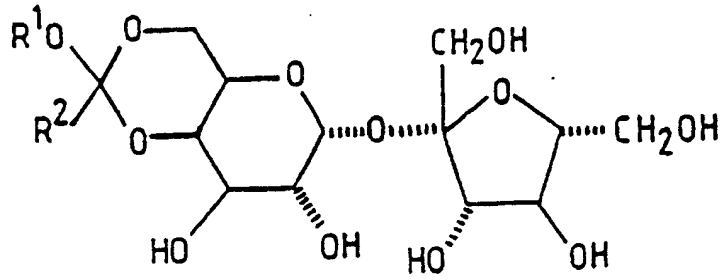
Sucrose 6-acetate	(carbon atom)	Sucrose
170.5	-CO-CH_3	-
103.9	2' -	104.4
91.5	1	92.4
82.8	5' -	82.8
77.0	3' -	77.4
74.6	4' -	74.7
72.8	3-	73.3
71.6	2-	72.0
70.3*	5-	73.3*
70.0	4-	70.2
63.9*	6-	60.9*
62.7	6' -	62.6
62.3	1' -	62.4
20.8	-CO-CH_3	

* significant difference

Claims

1. A sucrose alkyl 4, 6-orthoacylate.

2. A compound according to claim 1 of the general formula



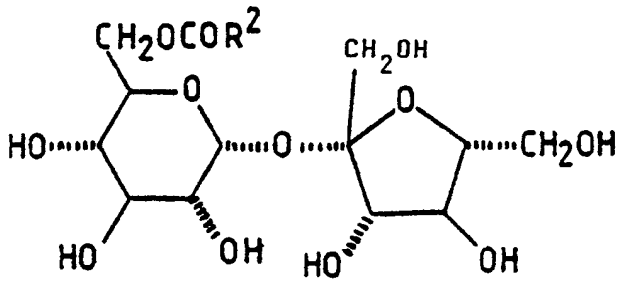
where R^1 represents an alkyl group, and R^2 represents an alkyl or aryl group.

3. A compound according to claim 1 or claim 2 selected from sucrose methyl 4,6-orthoacetate, sucrose ethyl 4,6-orthoacetate, sucrose methyl 4,6-orthobutyrate and sucrose methyl 4,6-orthobenzoate.

4. A method of preparing a sucrose alkyl 4,6-orthoacylate comprising reacting sucrose in solution or suspension in an inert organic solvent with a trialkyl orthoacylate in the presence of an acid catalyst.

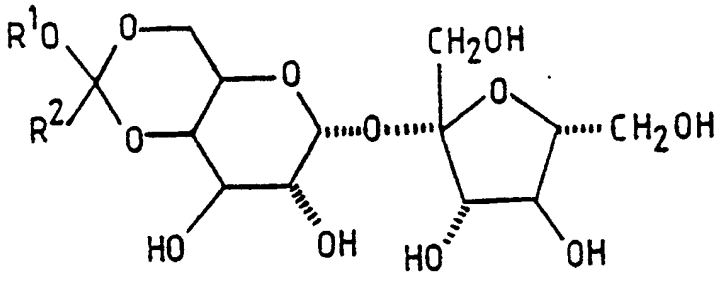
5. A process for the preparation of a sucrose 6-acylate comprising the steps of subjecting a sucrose alkyl 4, 6-orthoacylate according to claim 1 to mild aqueous acidic hydrolysis to provide a mixture of 4- and 6- monoesters of sucrose and then treating the ester mixture with a base to convert the sucrose 4-ester into sucrose 6-ester.

6. A process according to claim 5 for the preparation of a sucrose ester of the general formula II



(II)

in which R^2 represents an alkyl or aryl group, by treatment of an orthoester of the general formula I



(I)

in which R^1 represents an alkyl group and R^2 is as defined for formula II, under mild aqueous acidic

conditions followed by treatment with a base.

7. A process according to claim 5 or claim 6 in which the mild aqueous acidic treatment is effected in an inert polar organic solvent containing water in an excess over the amount theoretically required.

8. A process according to any of claims 5 to 7, in which the base treatment is effected using a tertiary amine.

9. A process according to claim 8 in which the base treatment is effected in the same solution used for the acid treatment.

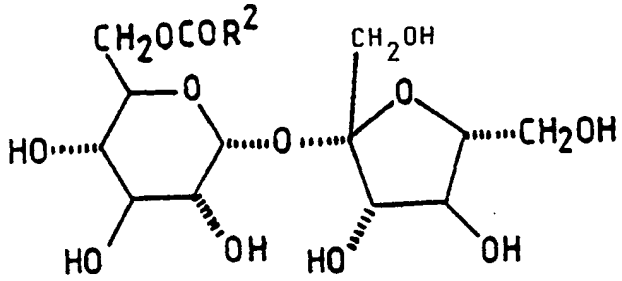
10. A process for the preparation of sucralose, by reacting a sucrose 6-ester with a chlorinating agent capable of effecting selective chlorination at the 4-, 1'-, and 6'- positions, optionally peresterifying the sucralose 6-ester so formed and deesterifying the sucralose ester before or after the separation from the reaction mixture, and recovering sucralose, characterised in that the formation of the sucrose 6-ester is effected by a process according to any of claims 5 to 9.

Claims for the following Contracting State: ES

1. A method of preparing a sucrose alkyl 4,6-orthoacylate comprising reacting sucrose in solution or suspension in an inert organic solvent with a trialkyl orthoacylate in the presence of an acid catalyst.

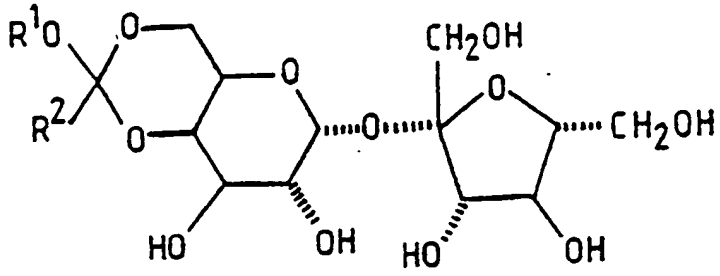
2. A process for the preparation of a sucrose 6-acylate comprising the steps of subjecting a sucrose alkyl 4, 6-orthoacylate according to claim 1 to mild aqueous acidic hydrolysis to provide a mixture of 4- and 6- monoesters of sucrose and then treating the ester mixture with a base to convert the sucrose 4-ester into sucrose 6- ester.

3. A process according to claim 2 for the preparation of a sucrose ester of the general formula II



(II)

in which R^2 represents an alkyl or aryl group, by treatment of an orthoester of the general formula I



(I)

in which R^1 represents an alkyl group and R^2 is as defined for formula II, under mild aqueous acidic

conditions followed by treatment with a base.

4. A process according to claim 2 or claim 3 in which the mild aqueous acidic treatment is effected in an inert polar organic solvent containing water in an excess over the amount theoretically required.

5. A process according to any of claims 2 to 4, in which the base treatment is effected using a tertiary amine.

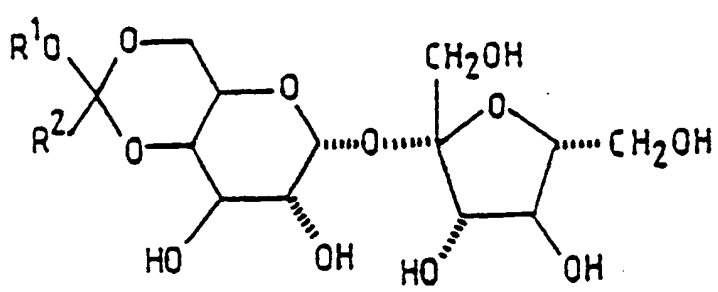
6. A process according to claim 5 in which the base treatment is effected in the same solution used for the acid treatment.

7. A process for the preparation of sucralose by reacting a sucrose 6-ester with a chlorinating agent capable of effecting selective chlorination at the 4-, 1' - and 6'- positions, optionally peresterifying the sucralose 6-ester so formed and deesterifying the sucralose ester before or after the separation from the reaction mixture, and recovering sucralose, characterised in that the formation of the sucrose 6-ester is effected by a process according to any of claims 2 to 6.

Revendications

1. Saccharose-alkyl-4,6-orthoacylate.

2. Composé selon la revendicaion 1 de formule générale



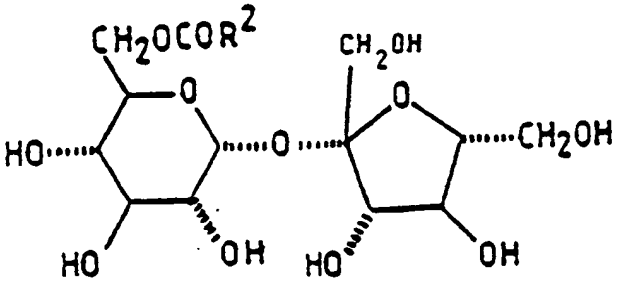
dans laquelle R^1 représente un groupement alkyle et R^2 représente un groupement alkyle ou aryle.

3. Composé selon la revendication 1 ou 2, choisi entre le saccharose-méthyl-4,6-orthoacétate, le saccharose-éthyl-4,6-orthoacétate, le saccharose-méthyl-4,6-orthobutyrate et le saccharose-méthyl-4,6-orthobenzoate.

4. Procédé de préparation d'un saccharose-alkyl-4,6-orthoacylate, consistant à faire réagir du saccharose en solution ou en suspension dans un solvant organique inerte avec un orthoacylate de trialkyle en présence d'un catalyseur acide.

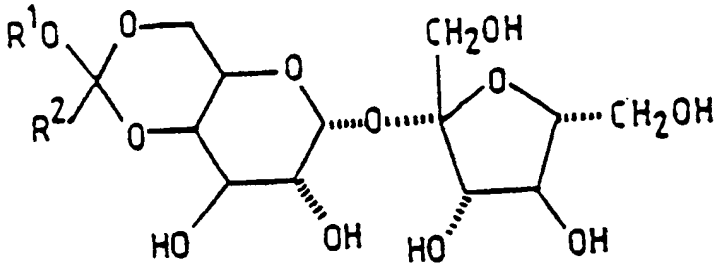
5. Procédé de préparation d'un saccharose-6-acylate comprenant les étapes consistant à soumettre un saccharose-alkyl-4,6-orthoacylate selon la revendication 1 à une hydrolyse acide aqueuse modérée pour former un mélange des 4- et 6-monoesters de saccharose puis à traiter le mélange d'esters par une base pour transformer le saccharose-4-ester en saccharose-6-ester.

6. Procédé selon la revendication 5 pour la préparation d'un ester de saccharose de formule générale II



(II)

dans laquelle R^2 représente un groupement alkyle ou aryle, par traitement d'un orthoester de formule générale I



(I)

dans laquelle R^1 représente un groupement alkyle et R^2 est tel que défini pour la formule II, dans des conditions acides aqueuses modérées, suivi d'un traitement par une base.

7. Procédé selon la revendication 5 ou 6, dans lequel le traitement acide aqueux modéré est effectué dans un solvant organique polaire inerte contenant de l'eau en excès par rapport à la quantité théoriquement requise.

8. Procédé selon l'une quelconque des revendications 5 à 7, dans lequel le traitement par une base est effectué en utilisant une amine tertiaire.

9. Procédé selon la revendication 8, dans lequel le traitement par une base est effectué dans la solution même utilisée pour le traitement acide.

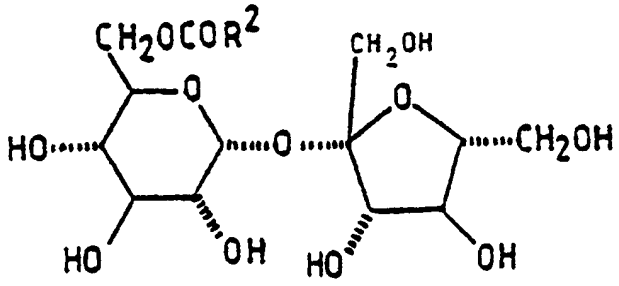
10. Procédé de préparation de sucralose, par réaction d'un saccharose-6-ester avec un agent de chloration pouvant effectuer une chloration sélective aux positions 4, 1' et 6', par perestérification facultative du sucralose-6-ester ainsi formé et désestérification de l'ester de sucralose avant ou après séparation d'avec le mélange réactionnel, et récupération du sucralose, caractérisé en ce que la formation du sucralose-6-ester est effectuée par un procédé selon l'une quelconque des revendications 5 à 9.

Revendication pour l'Etat contractant suivant: ES

1. Procédé de préparation d'un saccharose-alkyl-4,6-orthoacylate, consistant à faire réagir du saccharose en solution ou en suspension dans un solvant organique inerte avec un orthoacylate de trialkyle en présence d'un catalyseur acide.

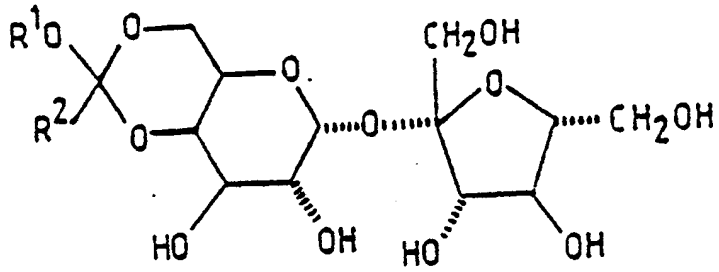
2. Procédé de préparation d'un saccharose-6-acylate comprenant les étapes consistant à soumettre un saccharose-alkyl-4,6-orthoacylate selon la revendication 1 à une hydrolyse acide aqueuse modérée pour former un mélange des 4- et 6-monoesters de saccharose puis à traiter le mélange d'esters par une base pour transformer le saccharose-4-ester en saccharose-6-ester.

3. Procédé selon la revendication 2, pour la préparation d'un ester de saccharose de formule générale II



(II)

dans laquelle R^2 représente un groupement alkyle ou aryle, par traitement d'un orthoester de formule générale I



(I)

dans laquelle R^1 représente un groupement alkyle et R^2 est tel que défini pour la formule II, dans des conditions acides aqueuses modérées, suivi d'un traitement par une base.

4. Procédé selon la revendication 2 ou 3, dans lequel le traitement acide aqueux modéré est effectué dans un solvant organique polaire inerte contenant de l'eau en excès par rapport à la quantité théoriquement requise.

5. Procédé selon l'une quelconque des revendications 2 à 4, dans lequel le traitement par une base est effectué en utilisant une amine tertiaire.

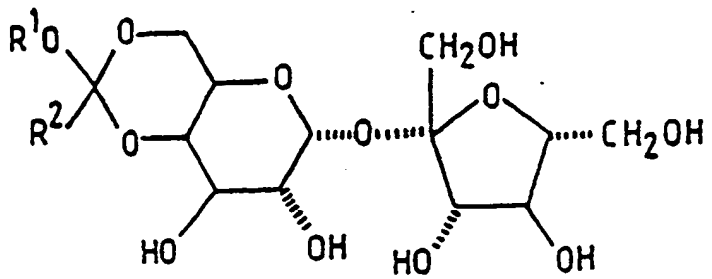
6. Procédé selon la revendication 5, dans lequel le traitement par une base est effectué dans la solution même utilisée pour le traitement acide.

7. Procédé de préparation de sucralose, par réaction d'un saccharose-6-ester avec un agent de chloration pouvant effectuer une chloration sélective aux positions 4, 1' et 6', par perestérification facultative du sucralose-6-ester ainsi formé et désestérification de l'ester de sucralose avant ou après séparation d'avec le mélange réactionnel, et récupération du sucralose, caractérisé en ce que la formation du sucralose-6-ester est effectuée par un procédé selon l'une quelconque des revendications 2 à 6.

Ansprüche

1. Ein Saccharose-alkyl-4,6-orthoacylat.

2. Verbindung nach Anspruch 1, welche die allgemeine Formel



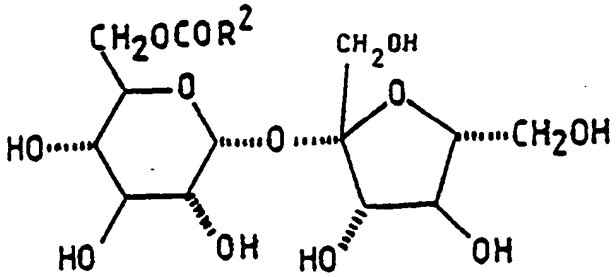
besitzt, in welcher R^1 eine Alkylgruppe bedeutet und R^2 eine Alkyl- oder Arylgruppe darstellt.

3. Verbindung nach Anspruch 1 oder Anspruch 2, welche aus Saccharose-methyl-4,6-orthoacetat, Saccharose-äthyl -4,6-orthoacetat, Saccharose-methyl-4,6-orthobutyrat und Saccharose-methyl-4,6-orthobenzoat ausgewählt ist.

4. Verfahren zum Herstellen eines Saccharose-alkyl -4,6-orthoacylats, bei welchem Saccharose in einem inerten organischen Lösungsmittel gelöst oder suspendiert in Anwesenheit eines Säurekatalysators mit einem Trialkyl -orthoacylat umgesetzt wird.

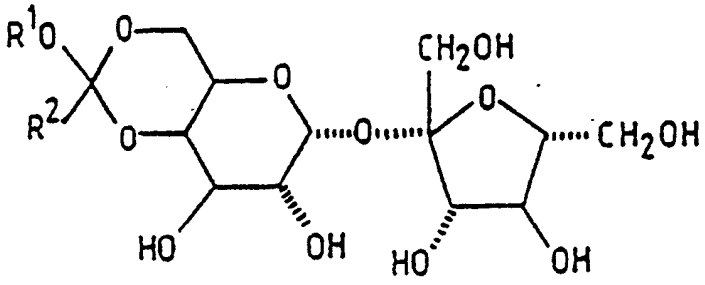
5. Verfahren zum Herstellen eines Saccharose-6-acylats, bei welchem ein Saccharose-alkyl-4,6-orthoacylat der in Anspruch 1 beanspruchten Art einer schwachen Hydrolyse in wässeriger Säure unterworfen und in ein Gemisch des 4-Monoesters und des 6-Monoesters von Saccharose übergeführt wird und anschließend das Estergemisch mit einer Base behandelt wird, um den Saccharose-4-ester in Saccharose-6 -ester überzuführen.

6. Verfahren nach Anspruch 5 zum Herstellen eines Saccharoseesters der allgemeinen Formel II



, (II)

in welcher R^2 eine Alkyl- oder Arylgruppe bedeutet, durch Behandeln eines Orthoesters der allgemeinen Formel I



(I)

in welcher R^1 eine Alkylgruppe bedeutet und R^2 die für Formel II angegebene Bedeutung besitzt, unter schwach sauren wässerigen Bedingungen und anschließendes Behandeln mit einer Base.

7. Verfahren nach Anspruch 5 und Anspruch 6, bei welchem die Behandlung mit schwacher wässeriger Säure in einem inerten, polaren organischen Lösungsmittel vorgenommen wird, welches Wasser im Überschuß über die theoretisch erforderliche Menge enthält.

8. Verfahren nach irgendeinem der Ansprüche 5 bis 7, bei welchem die Behandlung mit der Base unter Verwendung eines tertiären Amins vorgenommen wird.

9. Verfahren nach Anspruch 8, bei welchem die Behandlung mit der Base in der gleichen Lösung vorgenommen wird wie sie für die Behandlung mit der Säure verwendet wurde.

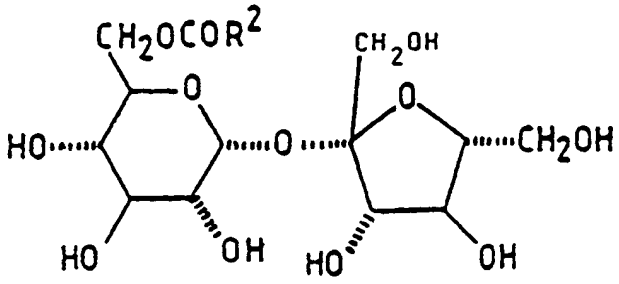
10. Verfahren zum Herstellen von Sucralose durch Umsetzen eines Saccharose-6-esters mit einem zu einer selektiven Chlorierung in 4-, 1'- und 6'-Stellung befähigten Chlorierungsmittel, durch gegebenenfalls vorzunehmendes Perverestern des so hergestellten Sucralose-6-esters und Abspalten der Estergruppe aus dem Sucraloseester vor oder nach dem Abtrennen aus dem Reaktionsgemisch und Gewinnen der Sucralose, dadurch gekennzeichnet, daß der Saccharose-6 -ester nach einem Verfahren gemäß irgendeinem der Ansprüche 5 bis 9 hergestellt wird.

Patentansprüche für folgenden Vertragsstaat: ES

1. Verfahren zum Herstellen eines Saccharose-alkyl -4,6-orthoacylats, bei welchem Saccharose in einem inerten organischen Lösungsmittel gelöst oder suspendiert in Anwesenheit eines Säurekatalysators mit einem Trialkyl -orthoacylat umgesetzt wird.

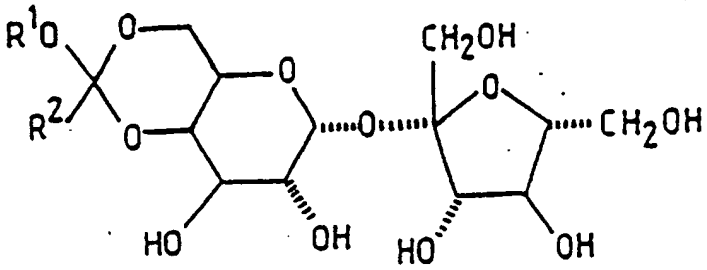
2. Verfahren zum Herstellen eines Saccharose-6-acylats, bei welchem ein Saccharose-alkyl-4,6-orthoacylat der in Anspruch 1 angegebenen Art einer schwachen Hydrolyse in wässeriger Säure unterworfen und in ein Gemisch des 4-Monoesters und des 6-Monoesters von Saccharose übergeführt wird und anschließend das Estergemisch mit einer Base behandelt wird, um den Saccharose-4-ester in Saccharose-6-ester überzuführen.

3. Verfahren nach Anspruch 2 zum Herstellen eines Saccharoseesters der allgemeinen Formel II



, (II)

in welcher R^2 eine Alkyl- oder Arylgruppe bedeutet, durch Behandeln eines Orthoesters der allgemeinen Formel I



(I)

in welcher R^1 eine Alkylgruppe bedeutet und R^2 die für Formel II angegebene Bedeutung besitzt, unter schwach sauren wässerigen Bedingungen und anschließendes Behandeln mit einer Base.

4. Verfahren nach Anspruch 2 oder Anspruch 3, bei welchem die Behandlung mit schwacher wässeriger Säure in einem inerten, polaren organischen Lösungsmittel vorgenommen wird, welches Wasser im Überschuß über die theoretisch erforderliche Menge enthält.

5. Verfahren nach irgendeinem der Ansprüche 2 bis 4, bei welchem die Behandlung mit der Base unter Verwendung eines tertiären Amins vorgenommen wird.

6. Verfahren nach Anspruch 5, bei welchem die Behandlung mit der Base in der gleichen Lösung vorgenommen wird wie sie für die Behandlung mit der Säure verwendet wurde.

7. Verfahren zum Herstellen von Sucralose durch Umsetzen eines Saccharose-6-esters mit einem zu einer selektiven Chlorierung in 4-, 1'- und 6'-Stellung befähigten Chlorierungsmittel, durch gegebenenfalls vorzunehmendes Perverestern des so hergestellten Sucralose-6-esters und Abspalten der Estergruppe aus dem Sucraloseester vor oder nach dem Abtrennen aus dem Reaktionsgemisch und durch Gewinnen der Sucralose, dadurch gekennzeichnet, daß der Saccharose-6-ester nach einem Verfahren gemäß irgendeinem der Ansprüche 2 bis 6 hergestellt wird.